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Skin Cancer Development in Solid Organ Transplant Recipients in Switzerland (Swiss Transplant Cohort Study)

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Keywords

Basal cell carcinoma · Melanoma · Keratinocyte carcinoma · Organ transplant recipient · Organ transplantation · Skin cancer · Squamous cell carcinoma

Abstract

Importance: Skin cancer, in particular squamous cell carcinoma, is the most frequent malignancy among solid organ transplant recipients with a higher incidence compared to the general population. ***Objective:*** To determine the skin cancer incidence in organ transplant recipients in Switzerland and to assess the impact of immunosuppressants and other risk factors. ***Design:*** Prospective cohort study of solid organ transplant recipients in Switzerland enrolled in the Swiss Transplant Cohort Study from 2008 to 2013. ***Participants:*** 2,192 solid organ transplant recipients. ***Materials and Methods:*** Occurrence of first and subsequent squamous cell carcinoma, basal cell carcinoma, melanoma and other skin cancers after transplantation extracted from the Swiss Transplant Cohort Study database and validated by medical record review. Incidence rates were calculated for skin cancer overall and subgroups. The effect of risk factors on the occurrence of first skin cancer and recurrent skin cancer was calculated by the Cox proportional hazard model. ***Results:*** In 2,192 organ transplant recipients, 136 (6.2%) developed 335 cases of skin cancer during a median follow-up of 32.4 months, with squamous cell carcinoma as the most frequent one. 79.4% of skin cancer patients were male. Risk factors for first and recurrent skin cancer were age at transplantation, male sex, skin cancer before transplantation and previous transplantation. For a first skin cancer, the number of immunosuppressive drugs was a risk factor as well. ***Conclusions and Relevance:*** Skin cancer following solid organ transplantation in Switzerland is greatly increased with risk factors: age at transplantation, male sex, skin cancer before transplantation, previous transplantation and number of immunosuppressive drugs.

Trial Registration: the study is registered on Clinicaltrials.gov under the registration No. NCT02361229.

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Introduction

Skin cancer represents over one third of all cancer cases in Switzerland [1]. Basal cell carcinoma (BCC) is the most common cancer overall in Switzerland and most other countries [2, 3]. Squamous cell carcinoma (SCC) is the second-most frequent keratinocyte cancer following BCC [4]. Most keratinocyte carcinoma in the general population is indolent with a low mortality rate but causes relevant morbidity [2, 4]. In the setting of immunosuppression such as in organ transplant recipients (OTR), the incidence of keratinocyte cancers, in particular SCC, increases 65- to 250-fold compared to the general population, greatly impacting morbidity and mortality [2, 4–11].

Due to improvements in clinical management, advances in transplantation medicine and immunosuppressive medication, outcomes and survival after solid organ transplantation have improved over the last few years. This, however, leads to an increased incidence of cancers after solid organ transplantation [12, 13]. The Swiss Transplant Cohort Study (STCS) is a prospective cohort study screening all candidates for solid organ transplantation since 2008 and finally enrolling them at transplantation [14]. The enrolment rate exceeds 95% and thus reflects well the transplant recipient population in Switzerland [15]. Skin cancers are prospectively captured in the 4 categories of SCC, BCC, melanoma and other skin cancers and allow the association of these skin

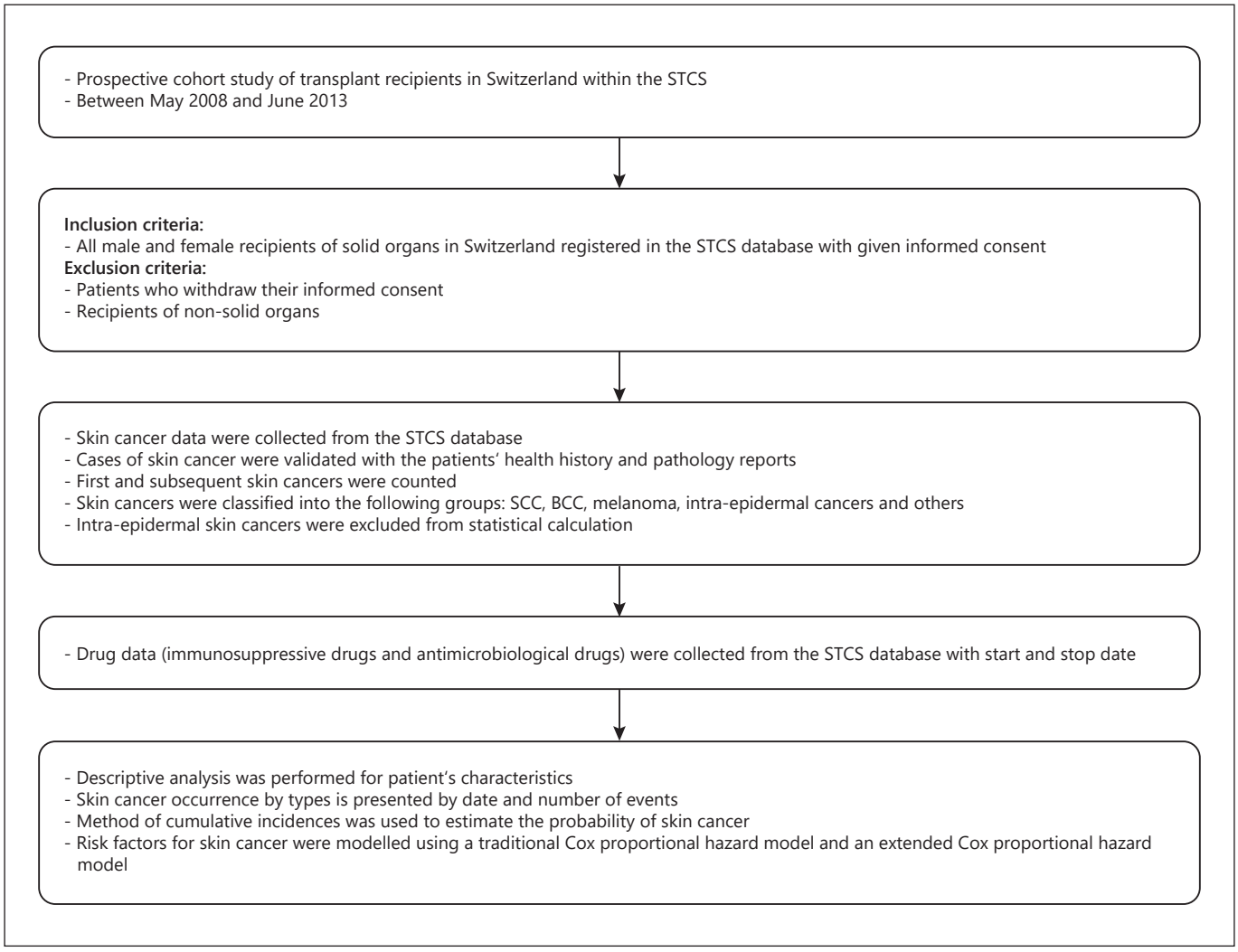

Fig. 1. Flowchart of Materials and Methods. STCS, Swiss Transplant Cohort Study; SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

Table 1. Patient characteristics

	Transplanted organ						
	kidney	liver	lung	heart	combined	other	all organs
Patients, *n* (%)	1,243 (56.7)	443 (20.2)	218 (9.9)	162 (7.4)	93 (4.3)	33 (1.5)	2,192 (100.0)
Male, *n* (%)	817 (65.7)	288 (65)	108 (49.5)	121 (74.7)	54 (58.1)	17 (51.5)	1,405 (64.1)
Median age at transplantation (IQR), years	53.4 (41.4–62.8)	54 (43.5–61.1)	55 (38.7–60.6)	51.8 (38.2–59.8)	44.4 (36.9–52.3)	51.3 (42.7–56.9)	53.2 (40.8–61.6)
Median follow-up time (IQR), months	36 (19.6–50.6)	28 (13.9–47)	26.7 (13.4–40.4)	27.4 (11.5–45.1)	32.4 (17.9–46.8)	42.2 (18.4–58.8)	32.4 (17.3–49)
Re-/second transplantation, *n* (%)	21 (1.7)	27 (6.1)	6 (2.8)	1 (0.6)	9 (9.7)	6 (18.2)	70 (3.2)
Previous transplantation, *n* (%)	210 (16.9)	21 (4.7)	8 (3.7)	1 (0.6)	12 (12.9)	23 (69.7)	275 (12.5)
Previous skin cancer, *n* (%)	60 (4.8)	8 (1.8)	9 (4.1)	3 (1.9)	1 (1.1)	5 (15.2)	86 (3.9)
Previous skin cancer + previous transplantation, *n* (%)							
Neither	1,007 (81)	415 (93.7)	204 (93.6)	158 (97.5)	80 (86)	10 (30.3)	1,874 (85.5)
Skin cancer, no previous transplantation	26 (2.1)	7 (1.6)	6 (2.8)	3 (1.9)	1 (1.1)	0 (0)	43 (2)
Previous transplantation, no skin cancer	176 (14.2)	20 (4.5)	5 (2.3)	1 (0.6)	12 (12.9)	18 (54.5)	232 (10.6)
Both	34 (2.7)	1 (0.2)	3 (1.4)	0 (0)	0 (0)	5 (15.2)	43 (2)
Death, *n* (%)	78 (6.3)	70 (15.8)	53 (24.3)	32 (19.8)	8 (8.6)	4 (12.1)	245 (11.2)
Drop-out, *n* (%)	8 (0.6)	3 (0.7)	1 (0.5)	1 (0.6)	1 (1.1)	2 (6.1)	16 (0.7)
Immunosuppressive medication, *n* (%)							
Glucocorticoid	1,242 (99.9)	416 (93.9)	217 (99.5)	157 (96.9)	93 (100.0)	23 (69.7)	2,148 (98)
AZA	124 (10.0)	23 (5.2)	9 (4.1)	50 (30.9)	12 (12.9)	7 (21.2)	225 (10.3)
MMF/EC-MPA	1,234 (99.3)	382 (86.2)	216 (99.1)	148 (91.4)	90 (96.8)	29 (87.9)	2,099 (95.8)
CNI	1,235 (99.4)	437 (98.6)	217 (99.5)	150 (92.6)	92 (98.9)	31 (93.9)	2,162 (98.6)
mTOR inhibitor	108 (8.7)	131 (29.6)	11 (5.0)	55 (34.0)	9 (9.7)	13 (39.4)	327 (14.9)
Infectious prophylaxis, *n* (%)							
Quinolone	213 (17.1)	41 (9.3)	50 (22.9)	6 (3.7)	7 (7.5)	0 (0.0)	317 (14.5)
Voriconazole	0 (0.0)	4 (0.9)	16 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	20 (0.9)

Transplanted organs were divided into kidney, liver, lung, heart, combined and other transplantation. Combined organ transplantations were transplantations of more than 1 organ at the same time and included 57 kidney and pancreas, 20 kidney and liver, 8 kidney and islet cells, 4 kidney and heart, 2 pancreas and small bowel transplantations, 1 liver and lung and 1 kidney, liver and islet cell transplantation. 21 double kidney transplantations were counted as kidney transplantation. Other transplanted organs included 1 small bowel, 9 pancreas and 23 islet cell transplantations. Retransplantation comprises second transplantations of the same organ during follow-up, while second transplantation stands for transplantation of a different organ during follow-up. Previous skin cancer includes patients with at least one skin cancer incident before inclusion into the STCS. Previous transplantation includes patients with previous transplants before inclusion into the STCS. Graft loss, death and drop-out comprise the whole follow-up time. n, number; IQR, interquartile range; AZA, azathioprine; MMF, mycophenolate mofetil; EC-MPA, enteric-coated mycophenolate acid; CNI, calcineurin inhibitor; mTOR inhibitor, mammalian/mechanistic target of rapamycin inhibitor.

Table 2. Skin cancer cumulative incidence

	Transplanted organ						
	kidney	liver	lung	heart	combined	other	all organs
Any skin cancer	92 (7.4)	15 (3.4)	14 (6.4)	6 (3.7)	3 (3.2)	6 (18.2)	136 (6.2)
Male	76 (82.6)	11 (73.3)	9 (64.3)	5 (83.3)	2 (66.7)	5 (83.3)	108 (79.4)
SCC	52 (4.2)	9 (2.0)	12 (5.5)	2 (1.2)	1 (1.1)	3 (9.1)	79 (3.6)
Male	42 (80.8)	8 (88.9)	8 (66.7)	1 (50.0)	1 (100.0)	2 (66.7)	62 (78.5)
BCC	56 (4.5)	9 (2.0)	2 (0.9)	5 (3.0)	2 (2.2)	3 (9.1)	77 (3.5)
Male	49 (87.5)	7 (77.8)	1 (50.0)	5 (100.0)	1 (50.0)	3 (100.0)	66 (85.7)
Melanoma	3 (0.2)	1 (0.2)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.3)
Male	3 (100.0)	1 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (100.0)
Other	1 (0.1)	2 (0.5)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)
Male	1 (100.0)	1 (50.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)
Median time to first skin cancer (IQR), months	13.9 (8.4–22.7)	14.2 (8.9–22)	15.6 (6.5–19.5)	15.2 (12.5–22.5)	11.9 (7.4–17.3)	18.2 (3.9–36.8)	14 (8.4–22.7)

Skin cancer cases were divided into 4 groups: squamous cell carcinoma (SCC), basal cell carcinoma (BCC), melanoma and other. Other includes dermal sarcoma, sarcoma not otherwise specified, sebaceous gland carcinoma, Kaposi sarcoma and atypical lymphocytic proliferation of T-cell type. The number and percentage of all skin cancers and the different groups of skin cancer were calculated, as well as the number and percentage of male patients with skin cancer. Combined organ transplantations were transplantations of more than one organ at the same time and included 57 kidney and pancreas, 20 kidney and liver, 8 kidney and islet cells, 4 kidney and heart, 2 pancreas and small bowel transplantations, 1 liver and lung and 1 kidney, liver and islet cell transplantation. 21 double kidney transplantations were counted as kidney transplantation. Other transplanted organs included 1 small bowel, 9 pancreas and 23 islet cells transplantations. IQR, interquartile range.

cancer events with a large data pool on the individuals affected [14].

The present study aims to report the incidence of skin cancer overall and by cancer type within the STCS in the years 2008–2013. We present descriptive statistics for these skin cancers and report associated risk factors based on the high granularity of data captured in the STCS.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000510685) (Fig. 1) [14, 16–18].

Results

Between May 2008 and June 2013, 2,192 patients with solid organ transplantation were included in our report. The median follow-up time was 32.4 months. Most of the patients (56.7%) were kidney transplant recipients, followed by liver, lung, heart, combined (i.e., kidney and pancreas) and other (i.e., pancreas, small bowel) transplant recipients. The median age at transplantation was 53.3 years, while 64.1% of the OTR were male. During follow-up 98% of the patients received glucocorticoids at least once, 10.3% azathioprine (AZA), 95.8% mycophenolate mofetil, 98.6% a calcineurin inhibitor and 14.9% a mammalian target of rapamycin (mTOR) inhibitor. 317 (14.5%) OTR were put on quinolones and 20 (0.9%) on voriconazole during our follow-up time. Full details are provided in Table 1.

As shown in Table 2 in detail, a total of 136 patients developed 335 cases of skin cancer during follow-up. 79 patients developed SCC, 77 BCC, 6 melanoma and 5 other skin malignancies (dermal sarcoma, sarcoma not otherwise specified, sebaceous gland carcinoma, Kaposi sarcoma, atypically lymphocytic proliferation T-cell type). The cumulative incidence reached 6.2% for any skin cancer, 3.6% for SCC and 3.5% for BCC. 79.4% of the OTR with skin malignancy were male. 186 of these 335 skin cancer cases were SCC, 137 BCC, 7 melanoma and 5 other skin malignancies. This results in an SCC-to-BCC ratio of 1.4:1. The median time to first skin cancer after transplantation was 14 months (Table 3).

Figure 2 shows the probability of incident skin cancer during follow-up. With time after transplantation, the probability of SCC and BCC increases while the number of patients at risk decreases over time. Figure 3 shows the distribution of skin cancer after transplantation itemized for each skin cancer type. Each OTR with skin cancer is represented by a horizontal line. In Figure 4a–c skin can-

Table 3. Skin cancer events

	Transplanted organ						
	kidney	liver	lung	heart	combined	other	all organs
Total number of skin cancer events, *n* (%)	**233 (69.5)**	**46 (13.7)**	**32 (9.6)**	**7 (2.1)**	**4 (1.2)**	**13 (3.9)**	**335 (100.0)**
Male, n (%)	211 (90.6)	42 (91.3)	27 (84.4)	6 (85.7)	3 (75.0)	12 (92.3)	301 (89.9)
Total number of SCC events, *n* (%)	**128 (68.8)**	**23 (12.3)**	**21 (11.3)**	**2 (1.1)**	**2 (1.1)**	**10 (5.4)**	**186 (100.0)**
Male, n (%)	116 (90.6)	22 (95.7)	17 (81.0)	1 (50.0)	2 (100.0)	9 (90.0)	167 (89.8)
Total number of BCC events, *n* (%)	**101 (73.7)**	**19 (13.9)**	**7 (5.1)**	**5 (3.6)**	**2 (1.5)**	**3 (2.2)**	**137 (100.0)**
Male, n (%)	91 (90.1)	17 (89.5)	6 (85.7)	5 (100.0)	1 (50.0)	3 (100.0)	123 (89.8)
Total number of melanoma events, *n* (%)	**3 (42.8)**	**2 (28.6)**	**2 (28.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**7 (100.0)**
Male, n (%)	3 (100.0)	2 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)
Total number of other events, *n* (%)	**1 (20.0)**	**2 (40.0)**	**2 (40.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**5 (100.0)**
Male, n (%)	1 (100.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)

Total number of skin cancer events during follow-up by transplanted organ and different skin cancer types. *n*, number; SCC, squamous cell carcinoma; BCC, basal cell number.

Table 4. Risk factors for first skin cancer overall

Risk factor	Reference	HR (95% CI)	*p* value
Age at transplantation	–	1.059 (1.04–1.079)	<0.001
Male sex	female sex	2.105 (1.36–3.259)	0.001
Previous skin cancer	no previous skin cancer	5.3 (3.446–8.152)	<0.001
Previous transplantation	no previous transplantation	2.211 (1.505–3.248)	<0.001
Number of immunosuppressive drugs	–	1.332 (1.022–1.736)	0.034

The risk factors for first skin cancer were calculated using multivariate analysis. –, lack of reference; HR, hazard ratio; 95% CI, 95% confidence interval; see also Figure 3, legend text.

Table 5. Risk factors for recurrent skin cancer

Risk factor	Reference	HR (95% CI)	*p* value
Age at transplantation (<2 years of transplant)	–	1.036 (1.008–1.064)	0.01
Age at transplantation (>2 years of transplant)	–	1.061 (1.029–1.094)	<0.001
Male sex	female sex	3.535 (2.234–5.595)	<0.001
Previous skin cancer (<2 years of transplant)	no previous skin cancer	9.413 (5.589–15.854)	<0.001
Previous skin cancer (>2 years of transplant)	no previous skin cancer	3.993 (1.565–10.189)	0.004
Previous transplantation (<2 years of transplant)	no previous transplantation	2.576 (1.657–4.003)	<0.001
Previous transplantation (>2 years of transplant)	no previous transplantation	1.634 (0.732–3.648)	0.231
Number of immunosuppressive drugs	–	1.160 (0.782–1.72)	0.46

The risk factors for recurrent skin cancer were calculated using multivariate analysis. –, lack of reference; HR, hazard ratio; 95% CI, 95% confidence interval.

cer cases per patient, classified into any skin cancer, SCC and BCC, are illustrated. The majority of patients suffered 1 or 2 skin cancer cases, but there is a noticeable minority with a large number of tumours, especially SCC.

Multivariate analysis showed age at transplantation, male sex, skin cancer before inclusion into the STCS, previous transplantation and number of immunosuppressive drugs as risk factors for the development of a first

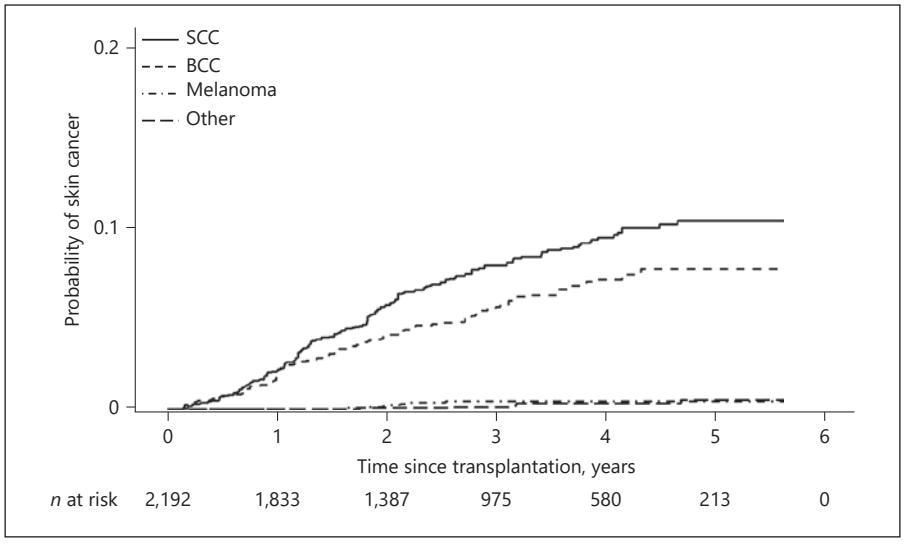

Fig. 2. Probability of incident skin cancer. Probability of incident skin cancer is displayed for squamous cell carcinoma (SCC), basal cell carcinoma (BCC), melanoma and other cancers over time and over number of patients at risk. "Other" includes dermal sarcoma, sarcoma not otherwise specified, sebaceous gland carcinoma, Kaposi sarcoma and atypical lymphocytic proliferation of T-cell type.

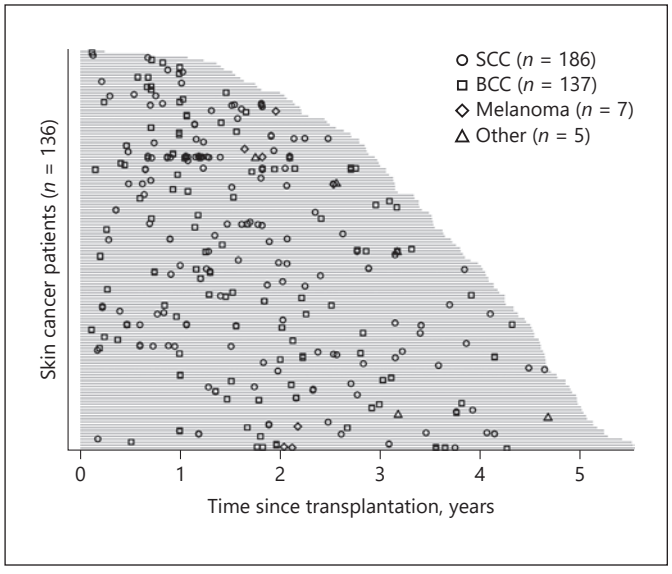

Fig. 3. Skin cancer events per patient after transplantation. Cases of skin cancer are displayed for squamous cell carcinoma (SCC) by open circles, basal cell carcinoma (BCC) by open squares, melanoma by open rhomboids and other cancers by open triangles over time. Grey bars represent the follow-up for each patient affected by skin cancer. "Other" includes dermal sarcoma, sarcoma not otherwise specified, sebaceous gland carcinoma, Kaposi sarcoma and atypical lymphocytic proliferation of T-cell type.

skin cancer overall (Table 4). For recurrent skin cancer, risk factors were age at transplantation, male sex, skin cancer before transplantation and also previous transplantation during the first 2 years after transplantation (Table 5). The number of immunosuppressive drugs was not significant for the development of recurrent skin cancer overall, neither in recurrent SCC nor BCC (Tables 6, 7).

Discussion and Conclusion

Our study reports the skin cancer incidence after transplantation of solid organs within the STCS. Our demographic results are comparable with previous studies. The median age in our study was slightly higher than in other studies, where age ranged between 41 and 53 years at transplantation [19–22]. As in our study, most OTR included in studies from the USA, Australia, Sweden, Norway and Denmark were male [8, 19–24]. The majority of our patients received a kidney transplant, followed by liver transplantation. Compared with our data, most studies showed a higher proportion of kidney transplant recipients around 76% [19–21]. Only one study from the USA showed a lower proportion of kidney transplant recipients of 48% [22]. Median follow-up and number of our enrolled patients were less than in similar studies, which included 5,279–10,649 patients with a median follow-up from 4 to 8 years [19–22]. With an enrolment rate of 95% of transplant recipients in Switzerland, our study population largely resembles the ones reported in other countries and is highly representative of the transplant population in Switzerland [15].

Garrett et al. [22] showed an incidence rate of 8% for posttransplantation skin cancer in the USA. Australian kidney transplant recipients showed skin cancer inci-

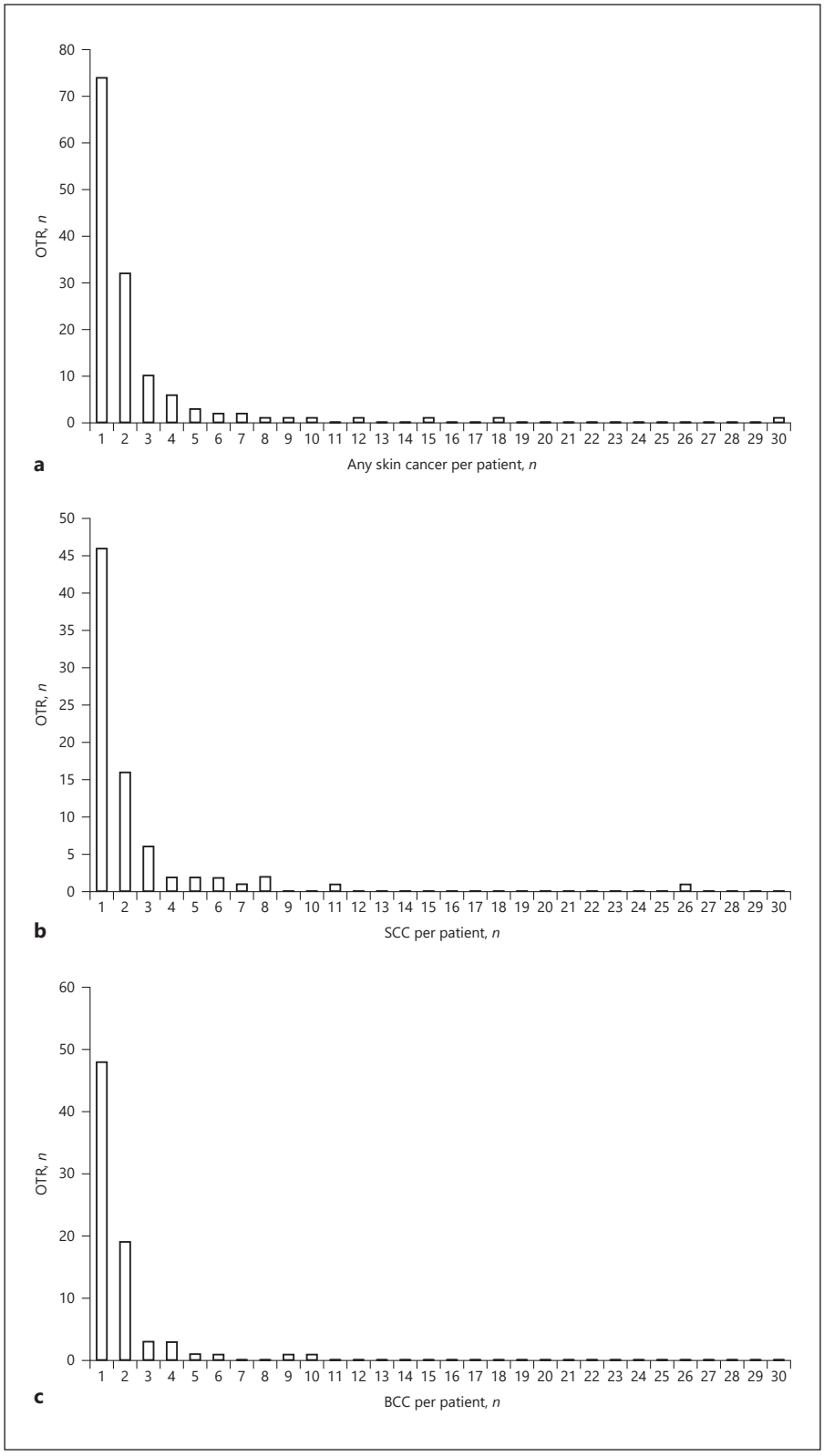

Fig. 4. a Number of skin cancers per patient. OTR, organ transplant recipients. The *y* axis shows the number of patients in relation to the number of skin cancers on the *x* axis. **b** Number of squamous cell carcinoma (SCC) per patient. The *y* axis shows the number of patients in relation to the number of squamous cell carcinoma (SCC) on the *x* axis. **c** Number of basal cell carcinoma (BCC) per patient. The *y* axis shows the number of patients in relation to the number of basal cell carcinoma (BCC) on the *x* axis.

Table 6. Risk factors for recurrent SCC

Risk factor	Reference	HR (95% CI)	*p* value
Age at transplantation (<2 years of transplant)	–	1.019 (0.985–1.054)	0.272
Age at transplantation (>2 years of transplant)	–	1.070 (1.035–1.106)	<0.001
Male sex	female sex	3.395 (1.912–6.028)	<0.001
Previous skin cancer (<2 years of transplant)	no previous skin cancer	14.523 (7.034–29.985)	<0.001
Previous skin cancer (>2 years of transplant)	no previous skin cancer	3.466 (1.521–7.899)	0.003
Previous transplantation (<2 years of transplant)	no previous transplantation	3.747 (2.08–6.751)	<0.001
Previous transplantation (>2 years of transplant)	no previous transplantation	2.027 (0.962–4.271)	0.063
Number of immunosuppressive drugs	–	1.174 (0.684–2.012)	0.561

The risk factors for recurrent squamous cell carcinoma (SCC) were calculated using multivariate analysis. –, lack of reference; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 7. Risk factors for recurrent BCC

Risk factor	Reference	HR (95% CI)	*p* value
Age at transplantation (<2 years of transplant)	–	1.060 (1.028–1.093)	<0.001
Age at transplantation (>2 years of transplant)	–	1.059 (1.014–1.106)	0.01
Male sex	female sex	3.605 (1.831–7.098)	<0.001
Previous skin cancer (<2 years of transplant)	no previous skin cancer	5.315 (3.22–8.776)	<0.001
Previous skin cancer (>2 years of transplant)	no previous skin cancer	5.009 (1.356–18.506)	0.016
Previous transplantation (<2 years of transplant)	no previous transplantation	1.437 (0.895–2.308)	0.133
Previous transplantation (>2 years of transplant)	no previous transplantation	1.399 (0.42–4.66)	0.584
Number of immunosuppressive drugs	–	1.148 (0.726–1.813)	0.555

The risk factors for recurrent basal cell carcinoma (BCC) were calculated using multivariate analysis. –, lack of reference; HR, hazard ratio; 95% CI, 95% confidence interval.

dences of 7, 25 and 79% after 1, 5 and 20 years of follow-up, respectively [8]. In Sweden the cumulative incidence of non-melanoma skin cancer (NMSC) after transplantation reached 6.7% after 10 years and 20.4% after 20 years of follow-up [25]. In an Italian registry-based study of kidney and heart transplant recipients, the cumulative incidence reached 5.8 and 10.8% 5 and 10 years after transplantation, respectively [26]. A Swiss long-term study of lung transplant recipients from 1992 till 2010 showed a cumulative incidence of SCC of 16.7 and 59.9% for 5 and 15 years after transplantation, respectively [27]. Except for NMSC in Sweden and Italy, our cohort reports lower incidence rates. This might be due to the shorter follow-up in our study, as skin cancer incidence in OTR seems to increase with duration of immunosuppression [8, 9, 28–30]. Our data show an increasing probability of incident skin cancer with time after transplantation, in particular for SCC (Fig. 2).

Compared to our tumour data, several publications – including only heart and/or renal transplant recipients – showed a much higher SCC-to-BCC ratio ranging between 2 and 7:1 [6, 7, 28, 31–34]. Studies including all solid transplant recipients from Israel and Denmark reported an SCC-to-BCC ratio of 1.9:1 [6] and 1:1, respectively [20], more in line with our data. Also studies from countries in southern Europe described lower SCC-to-BCC ratios of 1.1:1 in kidney transplant recipients in Portugal [35], 1.1:1 in Italian heart and 2.6:1 in Italian kidney transplant recipients [26]. For the general population in Switzerland, only the Canton of Vaud reports numbers which show the SCC-to-BCC ratio at 1:2.5 in the period between 1976 and 1992 [3]. The ratio of SCC to BCC in our present study might result from a rather short follow-up where the impact of previous sun damage before transplantation is still relatively predominant, while we expect an increase in the SCC-to-BCC ratio with a longer follow-

up. Since AZA is known to increase especially the risk for SCC [36], another explanation for the lower SCC-to-BCC ratio in our study might be the low percentage of patients in our cohort receiving AZA compared to other similar cohorts, where the majority of the patient had AZA as component of their maintenance immunosuppressive therapy [7, 31–33].

Previous data showed that risk factors for NMSC after transplantation are age at transplantation, male sex, history of pretransplantation skin cancer, type of transplanted organ, high sun exposure and fair skin type [8–10, 19, 22, 26–28, 33, 37, 38]. Our study finds correspondingly age at transplantation, male sex, previous skin cancer and additionally previous transplantation as risk factors for first and recurrent skin cancer. The duration of immunosuppression correlates with the increased skin cancer risk after transplantation, while the type of immunosuppressive drug seems an important risk factor [7, 8, 10, 31, 33, 39]. Dantal et al. [40] demonstrated in 1998 that more kidney transplant recipients developed a malignant disorder on a normal-dose cyclosporine regimen compared to patients on a low-dose cyclosporine regimen. There were also more patients with multiple skin lesions in the normal-dose cyclosporine group [40]. A change in immunosuppressive regimen from calcineurin inhibitor to mTOR inhibitor induced fewer NMSC [41, 42]. AZA increases UVA photosensitivity and subsequent photodamage, potentially leading to a higher skin cancer occurrence [43, 44]. Like many other studies we could not find an association for individual drugs with skin cancer. We did, however, find that the number of any immunosuppressive drugs is associated with the risk for a first skin cancer after transplantation, but not for recurrent skin cancer after transplantation. Our limited follow-up is the most likely limiting factor in associating skin cancer risk with individual immunosuppressants, followed by the limitation of our cohort data to the dose prescribed, not the trough levels achieved in serum. Selection bias for prescribing an mTOR inhibitor in high-risk individuals might also contribute. We hope that with a longer follow-up time, our cohort study will yield data on the impact of individual immunosuppressants.

OTR with previous skin cancer showed a higher hazard ratio for skin cancer in the first 2 years after transplantation compared to the period beyond 2 years. We believe that these findings show the decreasing impact of preexistent conditions in the course after transplantation. Previous skin cancer as a static risk factor tends to lose impact over time. Immunosuppression as dynamically increasing risk factor, however, gains impact over time, both in time after transplantation and by accumulated immunosuppressant use.

Limitations of our study are the limited number of skin cancer cases and the limited follow-up time of 36 months compared to similar studies. There is no matched control population because NMSC is not captured in the national cancer registry in Switzerland. Skin type and sun exposure, as well as serum levels of immunosuppressive drugs, were not captured in the STCS, precluding analysis of these factors for risk association.

Conclusion

In summary, our study is highly representative of the Swiss transplant recipient population. Skin cancer increases following transplantation with an important impact on morbidity and is associated with risk factors in our national cohort. Further follow-up will allow more granular dissection, for example, of individual immunosuppressants and their impact on skin cancer formation, potentially allowing immunosuppressive treatment regimes tailored to individual skin cancer risks in our transplant recipients.

Key Message

The incidence of skin cancer after organ transplantation is increased. We found some important risk factors.

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Statement of Ethics

All patients included in our report agreed to inclusion into the STCS for further use of their medical and personal data. This research project was approved by the Ethics Committee of Zurich, Switzerland (KEK-ZH-Nr. 2014-0276).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.A.S. was involved in concept, design, data collection, data analysis and interpretation, and writing of the article. G.F.L.H. contributed to concept, design, data analysis and interpretation, and writing of the article. S.S. performed data analysis and statistics. A.W.A., A.C., M.D., O.G., M.H., R.E.H., E.L., M.M. and M.N. contributed to data collection, interpretation and writing of the article.

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